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Impact of Body Mass Index on Cardiac Mortality in Patients With Known or Suspected Coronary Artery Disease Undergoing Myocardial Perfusion Single-Photon Emission Computed Tomography

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OBJECTIVES The purpose of this study was to assess the relationship between body mass index (BMI) and the prognostic value of myocardial perfusion single-photon emission computed tomography (MPS).

BACKGROUND The prognostic value of MPS in the obese has not been evaluated.

METHODS We studied 4,720 patients with and 10,019 patients without known coronary artery disease (CAD) who underwent rest Tl-201/stress Tc-99m sestamibi MPS, including 5,233 gated MPS studies and followed up (mean 2.7 to 3.2 years). Patients were categorized as normal weight (BMI 18.5 to 24.9 kg/m^2), overweight (BMI 25.0 to 29.9 kg/m^2), or obese (BMI $\geq$30.0 kg/m^2).

RESULTS Unadjusted annual rates of cardiac death (CD) rose versus stress MPS abnormalities in all weight groups ($p < 0.001$). Obese or overweight patients with or without known CAD who had normal MPS were at low CD risk (<1%/year), similar to normal weight patients. In CAD, obese and overweight patients with abnormal MPS had lower rates of CD compared with normal weight patients ($p < 0.01$). In patients with low ejection fraction (EF) by gated MPS, those with normal weight had highest CD rate ($p = 0.001$). Multivariable models revealed that BMI was not a predictor of CD in suspected CAD patients (hazard ratio [HR] 0.99; 95% confidence interval [CI] 0.95 to 1.02) but was an independent *inverse* predictor of CD in known CAD patients (HR 0.95; 95% CI 0.92 to 0.98), especially in women, adenosine stress, low EF, or abnormal perfusion.

CONCLUSIONS Normal MPS was associated with low risk of CD in patients of all weight categories. In patients with known CAD undergoing MPS, obese and overweight patients were at lower risk of CD over three years than normal weight patients. (J Am Coll Cardiol 2006;47: 1418–26) © 2006 by the American College of Cardiology Foundation

More than 65 million Americans are currently obese (1). Obesity is associated with an increased risk for cardiovascular disease and cardiac mortality in the general population (2–5). In several studies, however, higher body mass index (BMI) has been reported to correlate with greater survival among patients with chronic heart failure (CHF) (6,7), myocardial infarction (MI) (8), or coronary revascularization (9,10). Myocardial perfusion single-photon emission computed tomography (MPS) has been demonstrated to be effective for risk stratification in several subsets including women, elderly, diabetics, and so on (11–14). While a large proportion of patients undergoing stress MPS are overweight or obese, the relationship between patient weight and prognostic value of MPS has not yet been defined. Thus, the aim of this study was to assess the prognostic value of MPS in normal weight, overweight, and obese patients.

METHODS

Patient population. We evaluated 16,816 consecutive unique patients free of known non-ischemic cardiomyopathy or valvular heart disease who underwent rest thallium (Tl)-201/stress Tc-99m sestamibi dual-isotope MPS with exercise or adenosine stress between February 1991 and February 1999. All patients were prospectively enrolled in a registry, and follow-up data were obtained for at least one year after testing, after patients had given written informed consent for the procedure and follow-up portion of this study. Informed consent (including consent to participate in registry) was obtained at the time of stress testing. Of the initial population, 765 (4.5%) patients were lost to follow-up; 1,312 (7.6%) patients underwent early revascularization

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Abbreviations and Acronyms

BMI = body mass index
CABG = coronary artery bypass grafting
CAD = coronary artery disease
CHF = chronic heart failure
EDV = end-diastolic volume
EF = ejection fraction
ESV = end-systolic volume
LV = left ventricle/ventricular
LVEF = left ventricular ejection fraction
MPS = myocardial perfusion single-photon emission computed tomography
PCI = percutaneous coronary intervention
SPECT = single-photon emission computed tomography

(coronary artery bypass graft surgery [CABG] or percutaneous coronary intervention [PCI] ≤60 days after index MPS) and were excluded from this analysis, as previously described (15). Thus, the final population consisted of 14,739 patients (age 65 ± 13 years, 40% women) including 9,662 exercise and 5,077 adenosine stress. Of this total, 5,233 patients underwent gated MPS, 10,019 with suspected coronary artery disease (CAD) and 4,720 with known CAD (defined as history of MI or coronary revascularization).

BMI group classification. Patients were categorized by BMI [(weight in kg)/(height in meter)^2] as normal weight (BMI 18.5 to 24.9 kg/m^2, n = 5,715), overweight (BMI 25.0 to 29.9 kg/m^2, n = 6,102), or obese (BMI ≥30.0 kg/m^2, n = 2,922) (3,16). Weight and height were measured for all hospitalized patients and was self-reported by all others. Patients with low BMI (<18.5 kg/m^2, n = 291) were excluded due to the small size of the group and the high likelihood of serious comorbidities that could distort the prognostic relationships between BMI and MPS results. Regarding the 765 patients lost to follow-up, BMI distributions were 40%, 39%, and 21% from normal weight to obese categories, not significantly different from the study population.

Imaging and stress protocol. Patients were injected intravenously at rest with Tl-201 (3 to 4.5 mCi), and MPS was initiated 10 min after injection (17). Exercise or adenosine with or without low-level treadmill exercise protocols were then performed as previously described (12,17), with stress injection of Tc-99m sestamibi (25 to 40 mCi). Twelve-lead electrocardiography (ECG) was monitored during stress tests.

Patients with resting defects usually underwent 24-h redistribution Tl-201 MPS to assess reversibility. In patients studied after 1994, the post-stress acquisition employed gated MPS, and left ventricular (LV) ejection fraction (LVEF), end-systolic volume (ESV), and end-diastolic volume (EDV) were assessed using an automatic program (18).

Image interpretation and scintigraphic indexes. The summed stress scores (SSS) and summed rest scores (SRS) were obtained by adding the scores of 20 myocardial segments (19,20). Our database system required entry of a score for all 20 segments in each patient with no missing values. The sum of the differences between the SSS and SRS was defined as the summed difference score. These indexes were converted to percent of the total myocardium involved with stress, ischemic, or fixed defects by dividing the summed scores by 80, the maximum potential score (4 × 20), and multiplying by 100 (21). Stress defect <5%, 5% to 10%, and >10% myocardium were defined as normal, mildly, and moderately to severely abnormal scans (22). Because the presence and magnitude of hypoperfusion induced during adenosine MPS is roughly equivalent to the magnitude of ischemia induced during maximal exercise (23,24), we employ the term "inducible ischemia" to represent both the ischemia during exercise and adenosine MPS, even though actual ischemia is often not produced by the adenosine.

Follow-up data. All patients prospectively enrolled in the single-photon emission computed tomography (SPECT) registry are routinely followed through annual contact that was performed by experienced personnel for the determination of death status. This patient contact was made by mailed questionnaire followed by the use of a scripted blinded telephone interview in patients not initially responding to the mailing. Deaths were identified and confirmed through our hospital-based patient information system (WebVS) and the Social Security death index. To ascertain the cause of death, the information provided by WebVS and the death certificates were obtained for all who died in Los Angeles County and were reviewed consensually by two blinded experienced cardiologists. Cardiac death was defined as death from any cardiac cause (lethal arrhythmia, myocardial infarction, pump failure, etc.). Patients not confirmed to be deceased and without follow-up information (mail, telephone interview, or in WebVS) were considered lost to follow-up. The average length of follow-up was 3.2 ± 2.0 years and represented a positively skewed distribution of follow-up with the vast majority of values being within 1.0 to 4.5 years of follow-up.

Statistical analysis. All continuous variables are expressed as means ± SD. We performed univariate analyses of continuous variables using an unpaired *t* test. Univariable analyses of categorical variables were compared using the chi-square test. One-way analysis of variance with a post-hoc Bonferroni test was used to compare means of continuous variables among multiple groups. Pre-test likelihood of CAD was calculated by using CADENZA based on Bayesian analysis of pre-scan patient data (25). A probability value <0.05 was considered statistically significant. Cox proportional hazards analysis (version 10.0, SPSS Inc., Chicago, Illinois) was applied to identify univariable and multivariable estimators of cardiac death. Selection of variables for our multivariable models were based on univariable statistical significance of $p < 0.05$ as well as based upon clinical judgment. Age was included in our multivariable

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Table 1. Characteristics of Patients With Known CAD

	Normal Weight n = 1,865 (40%)	Overweight n = 2,029 (43%)	Obese n = 826 (18%)
Age (yrs)	71 ± 11*†	68 ± 11*	64 ± 11
≥70 yrs old	1,115 (60%)*†	961 (47%)*	273 (33%)
Gender (female)	556 (30%)*†	463 (23%)*	297 (36%)
Hypertension	853 (46%)*†	1,088 (54%)*	529 (64%)
Diabetes	294 (16%)*†	388 (19%)*	272 (33%)
Hypercholesterolemia	940 (50%)*†	1,097 (54%)	474 (57%)
Smoking	216 (12%)	271 (13%)	119 (14%)
Digoxin use	266 (14%)*†	160 (8%)	68 (8%)
Atrial fibrillation	88 (5%)*†	63 (3%)	19 (2%)
Angina	865 (46%)*	999 (49%)*	450 (54%)
Shortness of breath	165 (9%)	141 (7%)	65 (8%)
Resting heart rate	69 ± 13*	69 ± 13*	71 ± 13
Abnormal resting ECG	1,559 (84%)	1,677 (83%)	689 (83%)
Exercise test	1,100 (59%)	1,208 (60%)	465 (56%)
Exercise duration (min)	7.2 ± 2.7*	7.0 ± 2.5*	6.4 ± 2.2
Ischemic exercise ECG	221 (20%)	259 (21%)	86 (18%)

Values are n (%) or mean ± SD. *p < 0.02 vs. obese; †p < 0.02 vs. overweight.
CAD = coronary artery disease; ECG = electrocardiogram.

models using decile categories. Based upon these models, we derived risk-adjusted probabilities of cardiac death and cumulative survival curves to compare normal weight, overweight, and obese patients.

RESULTS

Clinical characteristics. Compared to patients with suspected CAD, those with known CAD were more often of normal weight (40% vs. 38%, p = 0.021) and overweight (43% vs. 41%, p = 0.023) but less often obese (18% vs. 21%, p < 0.001) and very obese (BMI >40 kg/m^2 [1.2% vs. 2.1%, p < 0.001]) (Tables 1 and 2).

In the known CAD group (Table 1), obese or overweight patients were much younger, more frequently female, had shorter exercise duration, higher resting heart rate, and a greater frequency of hypertension, diabetes mellitus, hypercholesterolemia, and typical angina symptoms as compared to patients at a normal weight (p < 0.02). Normal weight patients more often used digoxin and had atrial fibrillation (p < 0.02). Of note, no significant difference was revealed by type of stress performed exercise or pharmacologic stress between weight groups (p = NS).

In the suspected CAD group (Table 2), the differences between the weight groups were similar to those in the CAD group, with the following exceptions: obese patients more often presented with shortness of breath and less frequently had exercise stress and ischemic exercise ECG when compared to other weight groups (p < 0.001). Additionally, normal weight patients had a lower pre-test likelihood of coronary disease (p = 0.001).

MPS results. Myocardial perfusion SPECT findings in patients with known and suspected CAD are shown in

Table 2. Characteristics of Patients With Suspected CAD

	Normal Weight n = 3,850 (38%)	Overweight n = 4,073 (41%)	Obese n = 2,096 (21%)
Age (yrs)	66 ± 13*†	63 ± 13*	61 ± 12
≥70 yrs old	1,669 (43%)*†	1,433 (35%)*	556 (27%)
Gender (female)	2,022 (53%)†	1,535 (38%)*	1,090 (52%)
Hypertension	1,492 (39%)*†	1,968 (48%)*	1,281 (61%)
Diabetes	351 (9%)*†	489 (12%)*	454 (22%)
Hypercholesterolemia	1,491 (39%)*†	1,796 (44%)	981 (47%)
Smoking	552 (14%)	553 (14%)	277 (13%)
Digoxin use	232 (6%)	185 (5%)	104 (5%)
Atrial fibrillation	94 (2%)	119 (3%)	60 (3%)
Angina	1,472 (38%)*†	1,673 (41%)*	971 (46%)
Shortness of breath	203 (5%)*	228 (6%)	153 (7%)
Resting heart rate	69 ± 13*†	70 ± 13*	73 ± 14
Abnormal resting ECG	2,226 (58%)	2,296 (56%)	1,245 (59%)
Exercise test	2,691 (70%)*	2,890 (71%)*	1,308 (62%)
Exercise duration (min)	7.3 ± 2.9*	7.4 ± 2.7*	6.4 ± 2.3
Ischemic exercise ECG	605 (22%)*	598 (21%)*	182 (14%)
Pre-test likelihood of CAD	0.34 ± 0.27*†	0.36 ± 0.28	0.37 ± 0.28

Values are n (%) or mean ± SD. *p < 0.02 vs. obese; †p < 0.02 vs. overweight.
CAD = coronary artery disease; ECG = electrocardiogram.

Table 3. Scintigraphic Characteristics and Cardiac Deaths

	Normal Weight	Overweight	Obese
Patients with known CAD	n = 1,865	n = 2,029	n = 826
Cardiac deaths	154 (8.3%)†	107 (5.3%)	35 (4.2%)
Abnormal perfusion	1,260 (68%)	1,387 (68%)	554 (67%)
Stress defects (% myo)	13.3 ± 13.2	13.3 ± 12.9	12.9 ± 12.9
Fixed defects (% myo)	6.7 ± 10.7*	5.8 ± 9.8	5.9 ± 9.7
Ischemic defects (% myo)	6.4 ± 7.9*	7.2 ± 8.5	6.8 ± 8.0
LV enlargement	433 (23%)	457 (23%)	193 (23%)
LVEF <45%	195/592 (33%)	196/640 (31%)	100/298 (34%)
LVEF (n = 1,530)	0.50 ± 0.17	0.51 ± 0.15	0.51 ± 0.16
EDV (n = 1,423)	112 ± 69	114 ± 61	122 ± 69
ESV (n = 1,423)	65 ± 62	63 ± 53	67 ± 58
Patients with suspected CAD	n = 3,850	n = 4,073	n = 2,096
Cardiac deaths	70 (1.8%)	71 (1.7%)	35 (1.7%)
Abnormal perfusion	713 (19%)	862 (21%)	425 (20%)
Stress defects (% myo)	2.7 ± 6.2*	3.2 ± 7.0	2.9 ± 6.4
Fixed defects (% myo)	0.5 ± 2.8*	0.7 ± 3.1	0.6 ± 2.5
Ischemic defects (% myo)	2.2 ± 5.2*	2.5 ± 5.7	2.3 ± 5.2
LV enlargement	221 (6%)	288 (7%)	148 (7%)
LVEF <45%	76/1,366 (6%)	96/1,462 (7%)	72/875 (8%)
LVEF (n = 3,703)	0.64 ± 0.12†	0.61 ± 0.12	0.61 ± 0.12
EDV (n = 3,499)	75 ± 36†	85 ± 38	90 ± 41*
ESV (n = 3,499)	30 ± 26†	36 ± 28	38 ± 32

Values are n (%) or mean ± SD. *$p < 0.02$ vs. overweight; †$p < 0.01$ vs. other groups.
CAD = coronary artery disease; EDV = end-diastolic volume; ESV = end-systolic volume; LV = left ventricle; LVEF = left ventricular ejection fraction; % myo = % of myocardium.

Table 3. The patients with known disease more frequently had abnormal MPS and had a greater frequency of fixed and ischemic perfusion defects than the patients with suspected CAD. Among the weight groups, however, there were no differences in the frequency of an abnormal MPS scan and visual LV enlargement across weight groups ($p > 0.20$). For those with suspected CAD, perfusion defects were also similar across the weight groups, although patients with normal weight and the obese had slightly smaller perfusion defects as compared to overweight patients. In patients with gated MPS, LVEF and LV volumes were also similar among weight groups in known CAD patients. In patients with suspected CAD, normal weight patients had higher mean ejection fraction (EF), lower EDV and ESV compared to overweight or obese patients ($p < 0.01$).

Outcome events. The follow-up duration was 3.2 ± 2.0 years for patients with known CAD, 2.7 ± 1.6 years for patients with suspected CAD, and 2.9 ± 1.2 years for patients with gated MPS. The numbers of cardiac deaths in these two populations are shown in Table 3. During follow-up, the cardiac death rate was significantly higher in the CAD group as compared to that in the suspected CAD group (6.3% vs. 1.8%, $p < 0.001$). In patients with and without known CAD, unadjusted annual rates of cardiac death increased in each weight category as the scan abnormality increased ($p < 0.001$) (Figs. 1 and 2). In the patients with normal MPS, the cardiac death rate was low (<1%) in all weight groups in patients with and without known CAD (Figs. 1 and 2). Of interest, among patients with known CAD who had mildly or moderately to severely abnormal MPS,

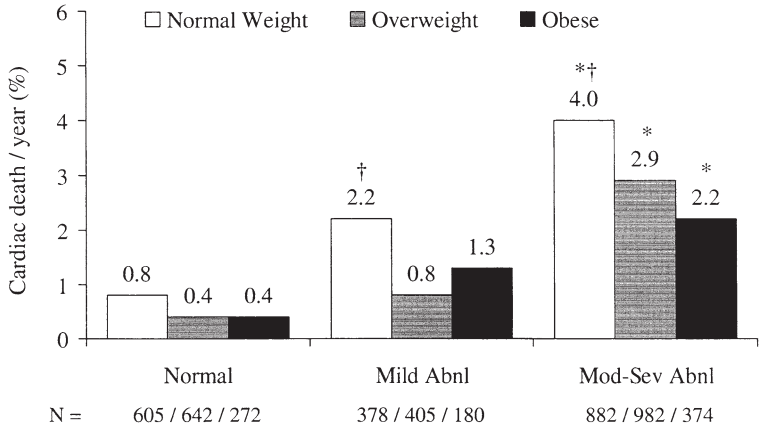

Figure 1. Annual rates of cardiac death in patients with known coronary artery disease by normal weight **(open bars)**, overweight **(gray bars)**, and obese **(black bars)** as a function of myocardial perfusion single-photon emission computed tomography results. *$p < 0.001$ across scan categories; †$p < 0.01$ across weight categories. Abnl = abnormal; Mod = moderate; Sev = severe.

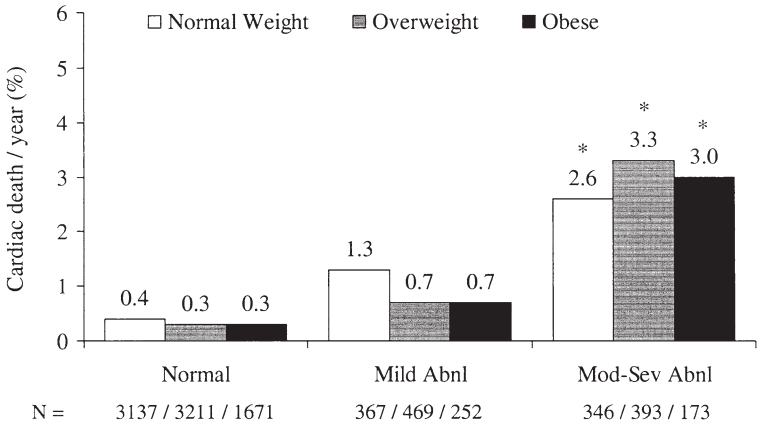

Figure 2. Annual rates of cardiac death in patients with suspected coronary artery disease by normal weight **(open bars)**, overweight **(gray bars)**, and obese **(black bars)** as a function of myocardial perfusion single-photon emission computed tomography results. *p < 0.001 across scan categories. Abnl = abnormal; Mod = moderate; Sev = severe.

those with normal weight had the highest rates of cardiac death (both p < 0.01). In patients with suspected CAD and abnormal scans, the rates of CD were similar across weight categories (p = NS).

In the subgroup of patients with gated MPS (Fig. 3), when the post-stress EF was ≥45%, cardiac death rates were low (<1%/year) regardless of weight category (p = NS). When EF was <45%, patients in each weight category had higher event rates than the patients with EF ≥45%. Importantly, among these patients with reduced EF, those with normal weight had twice the cardiac death rate as that of the heavier patients (p = 0.001).

Multivariable survival analysis. Significant predictors of cardiac death as based on Cox models in patients with known and suspected CAD are shown in Tables 4 and 5.

In patients with known CAD, adenosine stress was the strongest independent predictor followed by percent myocardium with stress defect and other significant predictors (Table 4). Both BMI and gender were independent predictors of cardiac death in this group; lower risk was noted with increasing BMI (p = 0.001) and in men (p = 0.033). Further, a significant interaction was present between these variables, such that BMI did not impact risk in men, but risk *decreased* with increasing BMI in women. The interaction between weight category and stress defect was also tested but was not significant.

In further assessment of the known CAD patients, there were 104 (2.2%) cardiac deaths occurring in the first year after MPS, including 57 (3.1%), 36 (1.8%), and 11 (1.3%) in the normal weight, overweight, and obese groups, respectively. During this first year, the cardiac death rate was significantly higher in the normal weight patients compared to patients in the other categories (p < 0.015 for both comparisons). Importantly, even when patients with these first-year cardiac deaths were excluded, BMI remained a significant reverse predictor of the 192 remaining cardiac deaths after adjusting for the other independent predictors (p = 0.011).

In patients with suspected CAD, percent myocardium at stress was the single greatest predictor, followed by age and adenosine stress, and other variables listed in Table 5. Body mass index was not an independent predictor for cardiac death (p = 0.26). There were no significant interactions revealed in this group.

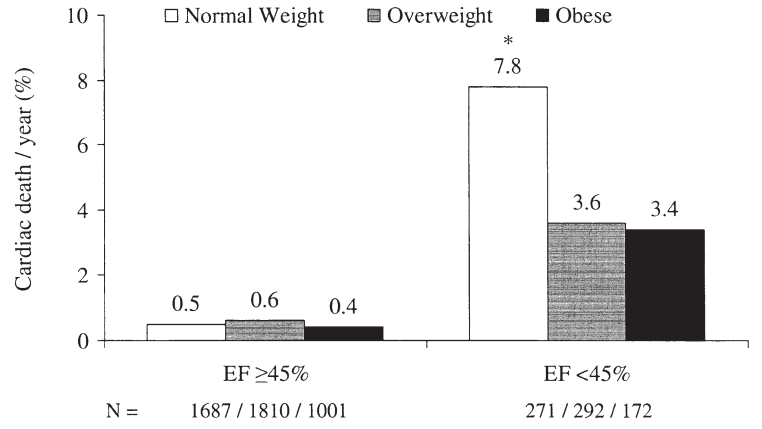

Figure 3. Annual rates of cardiac death in patients with gated myocardial perfusion single-photon emission computed tomography by normal weight **(open bars)**, overweight **(gray bars)**, and obese **(black bars)** in normal and abnormal ejection fraction groups. *p = 0.001 across weight categories. EF = ejection fraction.

Table 4. Multivariable Model for Prediction of Cardiac Death in Patients With Known CAD

	HR (95% CI)	Wald Chi-Square	p Value
Adenosine stress	2.94 (2.24–3.86)	59.9	0.000
% myo stress	1.02 (1.02–1.03)	28.2	0.000
Enlarged LV	2.05 (1.55–2.71)	25.8	0.000
Age by groups*	1.37 (1.21–1.56)	23.6	0.000
Rest heart rate	1.02 (1.01–1.03)	19.8	0.000
Hypercholesterolemia	0.67 (0.53–0.85)	10.4	0.001
Abnormal rest ECG	3.83 (1.69–8.70)	10.3	0.001
BMI	0.95 (0.92–0.98)	10.3	0.001
Shortness of breath	1.56 (1.16–2.10)	8.6	0.003
Digoxin use	1.52 (1.15–2.02)	8.6	0.003
Diabetes	1.45 (1.12–1.88)	8.1	0.004
Male gender	0.18 (0.04–0.87)	4.5	0.033
BMI × gender	1.07 (1.01–1.14)	4.9	0.026

*Age is categorized as <40, 40–49, 50–59, 60–69, 70–79, and ≥80 years old.
BMI = body mass index; CI = confidence interval; HR = hazard ratio; other abbreviations as in Tables 2 and 3.

For the models in Tables 4 and 5, gender, hypertension, smoking, family history of CAD, atrial fibrillation, angina symptom, ischemic stress ECG, and pre-test likelihood of CAD, as well as possible interactions, were analyzed and were not found to be significant predictors.

Risk-adjusted probabilities of cardiac death in BMI subgroups. Tables 6 and 7 detail three-year risk-adjusted rates of cardiac death as derived from the final multivariable model in patients with known CAD and suspected CAD by weight and MPS groups and other patient subsets. The predicted rates of cardiac death shown represent the average value for individuals in each group. In each BMI category, and in patients with suspected as well as known CAD, cardiac death rate increased as scan abnormality increased (Tables 6 and 7). In patients with known CAD (Table 6), there was a trend toward decreasing event rates as weight increased, particularly in patients with moderately to severely abnormal MPS, adenosine stress, lower LVEF, and elderly women. Cox proportional hazard analyses performed in these subgroups revealed the following: after adjusting for other significant predictors, lower BMI remained significant for predicting cardiac death in patients with abnormal MPS, adenosine stress, lower EF, women in both age groups ($p < 0.05$) but not in patients with normal MPS, exercise stress, EF ≥45%, or male gender ($p > 0.20$). Risk-adjusted probabilities of cardiac death were similar among weight categories in patients with suspected CAD (Table 7). Cox proportional hazard analysis confirmed that there were no significant differences between weight groups after risk adjustment ($p > 0.20$). Patients with lower EF and normal weight appeared to have a higher death probability than the heavier patients, but this difference was not significant, probably because of small number in this subgroup.

Outcomes in women. Risk-adjusted survival curves by categories of weight in women with known CAD and suspected CAD undergoing adenosine MPS are illustrated on Figures 4 and 5. Survival analysis was not performed in women undergoing exercise MPS due to a small number of cardiac deaths (n = 12). In women with known CAD, a significant decrease in survival was noted with decreasing weight after adjustment for other significant predictors

Table 5. Multivariable Model for Prediction of Cardiac Death in Patients With Suspected CAD

	HR (95% CI)	Wald Chi-Square	p Value
% myo stress	1.05 (1.04–1.06)	65.0	0.000
Age by groups*	1.64 (1.39–1.93)	34.4	0.000
Adenosine stress	2.65 (1.87–3.77)	29.6	0.000
Abnormal rest ECG	2.39 (1.48–3.88)	12.5	0.000
Enlarged LV	1.98 (1.33–2.96)	11.2	0.001
Shortness of breath	1.90 (1.29–2.79)	10.6	0.001
Diabetes	1.67 (1.19–2.34)	8.8	0.003
Digoxin use	1.69 (1.14–2.52)	6.7	0.010
Rest heart rate	1.01 (1.001–1.021)	4.5	0.034
BMI	0.98 (0.95–1.01)	1.3	NS

*Age is categorized as <40, 40–49, 50–59, 60–69, 70–79, and ≥80 years old.
Abbreviations as in Tables 2, 3, and 4.

Table 6. Three-Year Risk-Adjusted Rates of Cardiac Death in Patients With Known CAD by MPS Results, Gender, Age, Stress Type, and LVEF

	Normal Weight % (n)	Overweight % (n)	Obese % (n)
Normal	3.3 (605)	2.3 (642)	1.8 (272)
Mildly abnormal	5.3 (378)	4.5 (405)	3.3 (180)
Mod-Sev abnormal	12.0 (882)	8.5 (982)	6.3 (374)
Men	7.4 (1,309)	6.0 (1,566)	5.1 (529)
<70 yrs	4.2 (586)	3.8 (878)	4.2 (384)
≥70 yrs	10.0 (723)	8.8 (688)	7.4 (145)
Women	8.8 (556)	4.7 (463)	2.6 (297)
<70 yrs	3.6 (164)	2.7 (190)	2.2 (169)
≥70 yrs	10.9 (392)	6.1 (273)	3.2 (128)
Exercise	3.4 (1,100)	2.6 (1,208)	2.2 (465)
Adenosine stress	14.2 (765)	10.4 (821)	6.7 (361)
LVEF ≥45%	5.0 (397)	3.4 (444)	2.4 (198)
LVEF <45%	15.2 (195)	12.3 (196)	8.3 (100)

CAD = coronary artery disease; LVEF = left ventricular ejection fraction; Mod-Sev = moderately to severely; MPS = myocardial perfusion single-photon emission computed tomography.

Table 7. Three-Year Risk-Adjusted Rates of Cardiac Death in Patients With Suspected CAD by MPS Results, Gender, Age, Stress Type, and LVEF

	Normal Weight % (n)	Overweight % (n)	Obese % (n)
Normal	1.1 (3,137)	1.0 (3,211)	1.0 (1,671)
Mildly abnormal	3.0 (367)	2.2 (469)	2.4 (252)
Mod-Sev abnormal	7.5 (346)	7.8 (393)	6.1 (173)
Men	2.0 (1,828)	1.7 (2,538)	1.5 (1,006)
<70 yrs	0.7 (1,134)	0.8 (1,817)	0.9 (786)
≥70 yrs	4.1 (694)	4.1 (721)	3.8 (220)
Women	1.7 (2,022)	1.8 (1,535)	1.6 (1,090)
<70 yrs	0.6 (1,047)	0.8 (823)	0.9 (754)
≥70 yrs	2.9 (975)	3.0 (712)	3.2 (336)
Exercise	0.8 (2,691)	0.8 (2,890)	0.6 (1,308)
Adenosine stress	4.4 (1,159)	4.1 (1,183)	3.2 (788)
LVEF ≥45%	1.5 (1,290)	1.3 (1,366)	1.2 (803)
LVEF <45%	14.0 (76)	9.1 (96)	7.0 (72)

Abbreviations as in Table 6.

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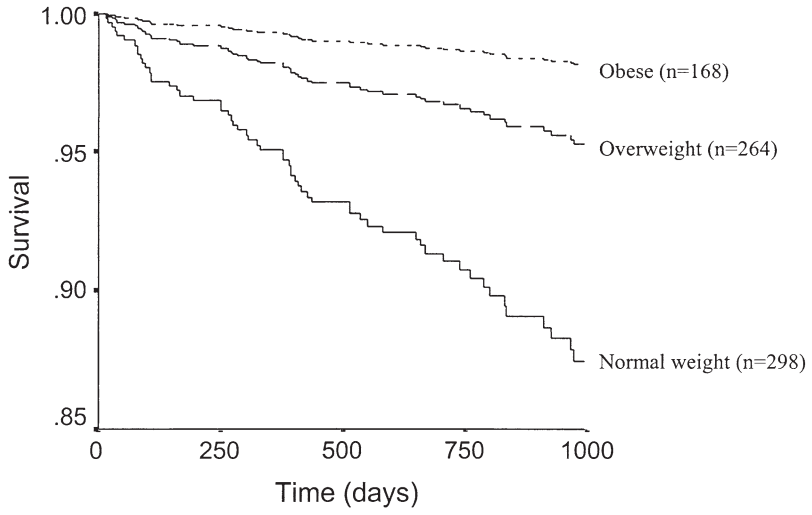

Figure 4. Risk-adjusted survival curves for cardiac death by categories of weights in women with known coronary artery disease undergoing adenosine myocardial perfusion single-photon emission computed tomography. Marked differences were noted, with the highest survival in obese women, and the lowest survival in normal weight women. $p < 0.001$ across groups.

including diabetes, hypercholesterolemia, LV enlargement, and stress defect percent, with the highest survival in obese women, the worst survival in normal weight women ($p < 0.001$ across groups) (Fig. 4). In women with suspected CAD, there were no significant differences in survival between obese and non-obese patients after adjusting for age, diabetes, resting ECG, and stress defect percent (Fig. 5).

DISCUSSION

To our knowledge, this is the first study that investigated the impact of weight as presented by BMI on cardiac death in patients undergoing rest and stress MPS. In this study of 14,739 patients, the findings indicate that obese or overweight patients with or without known CAD who had normal MPS were at low risk of cardiac death (<1% per year), similar to normal weight patients. The percent myocardium with stress defect was a strong predictor of cardiac death in all weight groups. Cardiac death rates rose uniformly as the percent myocardium with stress perfusion defects increased. Thus, our data demonstrate that MPS has a significant prognostic value for overweight and obese patients as well as for those of normal weight.

Of interest, in patients with known CAD, BMI was *inversely* related to cardiac death (i.e., an increased BMI is associated with a decreased risk of cardiac death); this was particularly notable for patients with abnormal MPS, low EF, undergoing adenosine stress, and women. Patients with CAD and lower BMI had significant higher risk of cardiac death than the other subsets. This significantly higher death rate was still observed when the first-year cardiac deaths were excluded, and was present when the first-year cardiac deaths were analyzed separately. Although normal weight

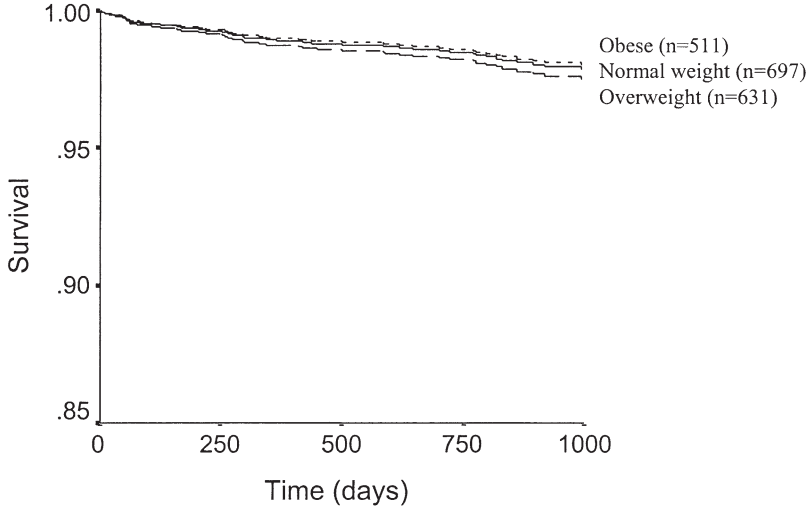

Figure 5. Risk-adjusted survival curves for cardiac death by categories of weights in women with suspected coronary artery disease undergoing adenosine myocardial perfusion single-photon emission computed tomography. There were no significant differences between obese and non-obese patients. p = NS for all comparisons.

patients were older than heavier patients, following risk-adjustment by age and other significant covariates, lower BMI remained independently predictive of cardiac death. However, BMI did not affect the risk of cardiac death in patients with suspected CAD.

Comparison to previous studies. Because this is the first report of the influence of obesity on the prognostic implications of MPS, there is no literature to directly compare the observations. While it is well known that obesity increases the risk of cardiovascular disease and mortality in the general population (2,3,26,27), this relationship is multifactorial and complex.

Our finding that BMI was inversely related to the rate of cardiac death in some subgroups is consistent with several other published observations (6–10,28,29). Obesity appears to be a "risk factor" for the development of CAD but possibly not a "risk marker" (29). Obesity has been reported to be less of a prognostic factor in patients with known CAD (8–10). In some prior observations, obesity has also been shown to be protective, and termed an "obesity paradox" (30) or "reverse epidemiology" (7). In a study of Horwich et al. (6), commented on by others (7,30), obesity was found to confer a favorable prognosis in patients with CHF. Lopez-Jimenez et al. (8) studied outcomes after MI and found that overweight and obese patients had a lower mortality compared to patients with normal weight. Recent data also have shown a possible protective effect of obesity on outcomes after PCI (9) or CABG (10). Minutello et al. (9) analyzed 95,435 patients undergoing PCI who with BMI 30 to 40 kg/m^2 had lower in-hospital mortality and major adverse cardiac events than lower weight patients. Gruberg et al. (10) reported overweight or obese patients had significantly better outcomes than those with normal BMI who underwent CABG.

Possible explanations for obesity being a reverse predictor of cardiac death in patients with known CAD. In the U.S., despite the growing prevalence of overweight and obese people (31), there has been a marked decline in cardiovascular mortality over the past 30 years (32,33). It is possible that an increase in CAD related to the increase in body weight has had little effect on recent mortality data as a result of more aggressive medical management and much lower levels of other coronary risk factors than in previous decades (34).

Several possible explanations for increased risk in patients with lower weight have been described. For example, in CHF, a malnutrition/inflammation complex syndrome has been postulated as conferring increased risk in patients with lower weights (6). These same investigators have suggested that a greater tolerance in obese and overweight patients of angiotensin-converting enzyme inhibitor therapy may be playing a protective role. A more likely explanation of the "obesity paradox" in our study is the difference between long-term and short-term risk. We evaluated relatively short-term mortality—mean follow-up time in the known CAD group was only 2.7 years. Obesity may confer a short-term survival benefit previously observed in post-MI, post-revascularization, and CHF cohorts, but at the same time might result in worsened long-term outcome; over a prolonged time, acceleration of the underlying cardiovascular disease process by obesity would be expected to become evident.

Study limitations. Current SPECT cameras have a maximal allowable weight of approximately 400 lbs. Accordingly, there were only 1% to 2% of patients with BMI >40 kg/m^2 in this study, and some severely obese who might have been at very high risk of mortality would not be included in this study. Our findings could have been related to a "survival bias." As a group, the normal weight patients were older and more often women than the heavier patients, especially in those with known CAD. The obese patients who live longer may represent the subset of the healthy obese. While the risk-adjusted analysis attempts to take these differences into account, they may still affect the results. Additionally, the existence of comorbidities and other prognostically important factors (i.e., physical activity, abdominal obesity, details of medical therapy) not recorded in our database, might have influenced the findings. Furthermore, a referral bias may be active such that obese patients with lower risk may be more likely to be referred for testing than normal weight patients of similar risk. Also, our results are based on a population referred for nuclear testing in a single center in Southern California and therefore may not be applicable to a broader population.

Gated MPS was performed only in the subset studied after 1994, because this approach was not available before that year. While it might be possible that increased artifacts due to soft tissue attenuation in the obese patients could have confounded the prognostic analysis of MPS, we have recently demonstrated that the size of perfusion defects and the diagnostic accuracy of MPS in our laboratory is not different between normal weight, overweight, and obese patients (35).

Conclusions. Stress defect by MPS is a strong predictor of cardiac death and valuable for risk stratification for those with a normal weight to obese patients. Patients who are overweight or obese and have normal MPS are at low risk for cardiac death. The rate of cardiac death rises as a function of MPS abnormality in all weight groups with and without known CAD. Body mass index does not affect the risk of cardiac death in patients with suspected CAD. Body mass index is an independent *inverse* predictor of cardiac death in patients with known CAD, with this effect being most marked in patients undergoing adenosine stress, having abnormal perfusion, or lower LVEF by MPS, and in women.

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